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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,707	04/20/2001	Angela M.I. Lam	16303-008110	2773

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/839,707	Lam
Examiner	**Art Unit**
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 4, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above, claim(s) *5, 18, 31, 36, 49, 62, and 64-67* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 6-17, 19-30, 32-35, 37-48, 50-61, 63, and 68* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☒ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *10*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election in the paper filed November 4, 2002, with traverse of Group I claims, claims 1-63, and 68, species of an endosomal membrane destabilizer being Ca^{2+} ion (claim 6), species of DODAC (claims 8 and 39), species of DOPE (claims 10 and 41), species of A-W-Y, wherein W is PEG (claims 13, 17, 44, and 48), A is a diacylglycerolyl moiety (claims 16, and 47), and Y is a lysine (claims 15 and 46), the species wherein the conjugated lipid that inhibits aggregation of particles has the formula II, wherein A is a diacyglycerolyl moiety having two fatty acyl chains, wherein each acyl chain is a saturated C-18 carbon chain (claims 20, 23, 24, 26, 51, 54, 55, and 57); Y is a cationic group having 4 lysine residues (claims 20, 23, 25, 26, 51, 54, 56, 57); X is a phosphoethanolamino (claims 20, 21, 23, 51, 54); and Z is NR, wherein R is hydrogen (claims 20, 22, 23, 51, 52, and 54); the species of PEG-ceramide (claims 27, 28, 58, 59), and the species of a nucleic acid being a plasmid (claims 32 and 63).

The traversal is that no serious undue burden can be established when examining all pending claims, the traversal is not found persuasive because of the reasons set forth in the restriction letter.

The restriction is proper, and thus, made final.

Claims 64-67 (non-elected group) and Claims 5, 18, 31, 36, 49, 62, directed to non-elected species have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 9, 33-34, 40, 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 33 are indefinite in the recitation of "said particle" because it is not apparent that the term does not have an antecedent basis, and because "a nucleic acid-lipid particle composition" is not the same as the "particle". Claims 2-3, 34, 40, 42 are indefinite because of the recitation of "said nucleic acid-lipid particle".

The term is not the same as "a nucleic acid–lipid particle composition" because the "composition" is not necessarily limited to "a nucleic acid-lipid particle", and because the "said nucleic acid-lipid particle" does not have any antecedent basis. Note also that it is not apparent as to how an endosomal membrane which is contained in the claimed composition of the base claim 1, for example, can also be claimed as being outside of the particle composition. Clarification is requested.

Claim 68 claims the use of a nucleic acid–lipid particle composition but, since the claims do not set forth any steps involved in the method/process, it is unclear what method, process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 68 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki,* 153 USQP 678 (Bd.App. 1967) and *Clinical Products, Ltd. V. Brenner,* 255 F. Supp. 131, 149 USPQ 475 (D.D.C., 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the

examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-15, 17, 19-22, 27-30, 32-35, 37-46, 48-53, 58-61, 63 are rejected under 35 USC 103(a) as being unpatentable over Bally *et al.* (US Pat No. 5,705,385) taken with either WO 98/19710 or Park *et al.* (US Pat No. 6,177,274, which claims priority under 119(e) to the provisional application 60/186,072, filed May 20, 1998, which provisional application is already provided to applicant in the '639 parent application), and further in view of either Haberland (Biochimica et Biophysica Acta 1445, 21-30, April 14, 1999) or Russell *et al.* (US Pat No. 6,270,761).

Bally teaches a SPLP particle comprising DODAC/DOPE and PEG-ceramide (a PEG derivatized lipid) which encapsulates a DNA, *e.g.,* plasmid encoding a protein of interest (entire column 7, column 8 bridging column 9, column 9, lines 30-38, column 11, lines 19-34, column 13, lines 5-7. In addition, column 10, last paragraph discloses that polycationic agents such as polylysine or salts can be added to the preformed particle so as to enhance the transfection of the particle to a cell of interest. As to the reduction of aggregation, column 12 bridging column 13 discloses that PEG or known derivatized lipids such as PEG-ceramide when added to the particle would prevent particle aggregation and provide a means for increasing circulation lifetime and increasing the delivery of the lipid-nucleic acid particles to the target tissues. Bally discloses that the polynucleotide can be a nucleic acid construct (plasmid) encoding a therapeutic protein. Column 10 discloses that the average size of the pre-formed liposome (second lipid) is typically between about 100nm and several microns. Column 11 discloses that one of the preferred MW for PEG is about 1000 daltons, that between 1-15 mole percent of such a derivatized lipid is included in the liposome formulation (column 13), and that preparation of vesicle-forming lipids derivatized with hydrophilic polymers has been described in US Pat No. 5820873.

Bally does not teach an incorporation of a polylysine to the PEG-lipid containing lipid conjugate, and of a cationic Ca^{++} ion as an endosomal disrupting agent in the SPLP particle containing composition, *e.g.,* inside and/or outside of the SPLP particle.

However, at the time the invention was made, the concept of utilizing a polycationic polylysine (PLL) linked to PEG, whereby PEG-PLL functions as an enhanced linker so as to link the backbone of PLL to a bioactive molecule or targeting ligand and to subsequently enhance the targeting efficiency of the bioactive molecule or the ligand to a cell of interest is well-taught in both the '710 reference (pages 9 and 10) and Park (columns 3 and 4). In addition, page 10 (lines 30-34) of the '710 reference teaches that a endosomal membrane disrupting agent once incorporated or linked to the reactive groups of the modified polymer, the agents would enable the DNA to gain access to the cytoplasm of the target cells. Also, Park *et al.* teach on columns 2 through 3 that PLL (polylysine) has been routinely employed as a condensing agent so as to increase intracellular delivery of a charged agent, and that PEG of MW 0.5-20 K MW linked to PLL even further enhances the delivery of a charged therapeutic agent across the bilayer membrane of a target cell (column 3 through column 4).

It would have been obvious for one of ordinary skill in the art to have linked one or more polycationic agent such as polylysine having more than at least between 4 and 15 positive charges to any PEG derivatized lipid or the PEG-ceramide contained in the particle of Bally with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to have incorporated a polycationic moiety(s) to the of the PEG-ceramide contained in the particle of Bally because the concept of utilizing a polycationic polylysine (PLL) linked to PEG, whereby PEG-PLL functions as an enhanced linker so as to link the backbone of PLL to a bioactive molecule or targeting ligand and to subsequently enhance the targeting efficiency of the bioactive molecule or the ligand to a cell of interest is well-taught in Park (columns 3 and 4), respectively, and because PEG linked to PLL even further enhances the delivery of a charged therapeutic agent across the bilayer membrane of a target cell.

Insofar as the limitation of an incoporation a cationic Ca^{++} ion in the SPLP particle containing composition, Russell teaches that calcium phosphate crystals when complexed with a delivery vector or agents that enhance the transfection of a nucleic acid to a cell, *e.g.,* membrane disrupting agents, the Ca^{2+} ion containing crystals enhance the delivery of a nucleic acid to a cell (abstract, column 3). Column 8 in Russell discloses that 5 mM of $CaCl^2$ can be employed in a nucleic acid delivery composition. In addition, Haberland further teaches that Ca^{++} ion is an efficient cofactor of polycation-mediated gene

transfer by functioned as an endosomal disrupting agent, abstract, entire page 28, and page 29.

It would have been obvious for one of ordinary skill in the art to have further incorporated Ca^{++} ion containing salt in a particulate form in the SPLP particle containing composition taught by the combined cited references. One of ordinary skill in the art of nucleic acid transfection would have been motivated to have employed a Ca^{++} ion containing salt in a particulate form in the SPLP particle containing composition because Russell teaches that calcium phosphate crystals when complexed with a delivery vector or agents that enhance the transfection of a nucleic acid to a cell, and because Haberland further teaches that Ca^{++} ion is an efficient cofactor of polycation-mediated gene transfer by functioned as an endosomal disrupting agent. One of ordinary skill in the art would also have expected that due to its small size and its affinity to negatively charged nucleic acids, the Ca^{++} ions are expected to gain access and complex with the negatively charged nucleic acids of the SPLP particle.

Thus, claimed invention as a whole was *prima facie* obvious.

Claims 1-4, 6-17, 19-30, 32-35, 37-48, 50-61, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bally *et al.* (US Pat No. 5,705,385) taken with either WO 98/19710 or Park *et al.* (US Pat No. 6,177,274, which claims priority under 119(e) to the provisional application 60/186,072, filed May 20, 1998, which provisional application is already provided to applicant in the '639 parent application), either Haberland (Biochimica et Biophysica Acta 1445, 21-30, April 14, 1999) or Russell *et al.* (US Pat No. 6,270,761), and further in view of Semple (US Pat No. 6287591).

The elected embodiment embraced by the pending claims is a lipid-based drug formulation comprising Ca^{++} ions on and/or in the SPLP particle, which further comprises a conjugate lipid comprising a diacyglycerolyl based PEG -polylysine-targeting ligand, wherein the polysine comprises at least 4 consecutive lysine residues for use in enhancing the delivery of a bioactive agent to cells of interest.

The rejection of the claimed embodiment readable on a lipid-based drug formulation comprising Ca^{++} ions on or in the SPLP particle, which further comprises a conjugate lipid comprising a derivatized lipid-PEG-polylysine-targeting ligand, wherein the polysine comprises at least 4 consecutive lysine residues is applied here as indicated above.

However, the combined cited references of Bally taken with either the '710 reference or Park, and either Haberland or Russell do not teach the derivatized lipid-PEG is a diacyglycerolyl based PEG, and that the conjugated lipid comprises a diacyglycerolyl based PEG -polylysine-targeting ligand.

However, at the time the invention was made, Semple teaches a liposome or vesicle forming lipid carrier comprising regular lipids and modified lipids, wherein the modified lipids are conjugated to a hydrophilic polymer for the purpose of enhancing intracellular delivery of the charged therapeutic agent(s) (entire document). More specifically, the preparation or lipid-based drug formulation of Semple (columns 12 bridging column 12 and column 14) comprises any known lipid carrier linked to a PEG-modified lipids including those of diacyglycerolyl based PEG, which can be used as a derivatized lipid in any lipid composition, would enhance the bioavailability of any charged nucleic acid entrapped in the lipid delivery composition.

It would have been obvious for one of ordinary skill in the art to employ the diacyglycerolyl based PEG as a linker, spacer to polylysine-targeting ligand and/or coating on the SPLP particle-based lipid delivery composition of the combined cited references. One of ordinary skill in the art would have been motivated to have employed the diacyglycerolyl based PEG as a linker, spacer or coating on the SPLP particle because Bally teaches that PEG or any known derivatized lipid when added to the particle would prevent particle aggregation and provide a means for increasing circulation lifetime and increasing the delivery of the lipid-nucleic acid particles to the target tissues, and because Semple teaches that any known lipid carrier linked to a PEG-modified lipids including those of diacyglycerolyl based PEG, which can be used as a derivatized lipid in any lipid composition, would also enhance the bioavailability of any charged nucleic acid entrapped in the lipid delivery composition.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the

conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-17, 19-30, 32-35, 37-48, 50-61, and 63 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-63 of US patent application 09/553,639 taken with Haberland (Biochimica et Biophysica Acta 1445, 21-30, April 14, 1999) or Russell *et al.* (US Pat No. 6,270,761).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are readable on a lipid-based drug formulation comprising an SLPL particle comprising a conjugate lipid comprising a diacyglycerolyl based PEG -polylysine-targeting ligand, wherein the polysine comprises at least 4 consecutive lysine residues for use in enhancing the delivery of a bioactive agent to cells of interest. Insofar as the limitation of an incoporation a cationic Ca^{++} ion in the SPLP particle containing composition, Russell teaches that calcium phosphate crystals when complexed with a delivery vector or agents that enhance the transfection of a nucleic acid to a cell, *e.g.,* membrane disrupting agents, the Ca^{2+} ion containing crystals enhance the delivery of a nucleic acid to a cell (abstract, column 3). Column 8 in Russell discloses that 5 mM of $CaCl^2$ can be employed in a nucleic acid delivery composition. In addition, Haberland further teaches that Ca^{++} ion is an efficient cofactor of polycation-mediated gene transfer by functioned as an endosomal disrupting agent, abstract, entire page 28, and page 29.

It would have been obvious for one of ordinary skill in the art to have further incorporated Ca^{++} ion containing salt in a particulate form in the SPLP particle containing composition as claimed in the claims of the '639 application One of ordinary skill in the art of nucleic acid transfection would have been motivated to have employed a Ca^{++} ion containing salt in a particulate form in the SPLP particle containing composition because Russell teaches that calcium phosphate crystals when complexed with a delivery vector or agents that enhance the transfection of a nucleic acid to a cell, and because Haberland further teaches that Ca^{++} ion is an efficient cofactor of polycation-mediated gene transfer by functioned as an

endosomal disrupting agent. One of ordinary skill in the art would also have expected that due to its small size and its affinity to negatively charged nucleic acids, the Ca^{++} ions are expected to gain access and complex with the negatively charged nucleic acids of the SPLP particle.

Thus, the claims of the '639 application and the examined claims are obvious variants of one another when taken with the cited prior art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The additional prior art as cited in the PTO-892, coupled with prior art cited in the IDS, particularly WO 98/51285, Mori, J. of Liposome Res., 8, 2, 195-211, 1998, WO 96/40964, Wheeler, Gene Therapy, 6, 271-281, 1999, Ouahabi *et al.,* FEBS letters, 414, 187-192, 1997, are additional support to the stated rejection to the extent that these prior art references provide evidence to show that the level of a person of one ordinary skill in the art of making serum stable lipids comprising a cationic lipid/phospholipid-PEG/polylysine/targeting ligand, which is capable of being release into the cytosol of a targeting cell, is high.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1633

DAVE T. NGUYEN
PRIMARY EXAMINER